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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/522,396	08/16/2005	Roger F. Bone	30923-713.833	6315

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EXAMINER	
LANDSMAN, ROBERT S	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/522,396	BONE ET AL.	
	Examiner	Art Unit	
	ROBERT LANDSMAN	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *1/24/05 (Preliminary Amendment)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *10-18,22-24,27,28 and 61-70* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *10-18,22-24,27,28 and 61-70* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *24 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/25/06; 4/18/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Formal Matters

A. The Preliminary Amendment filed 1/24/05 has been entered into the record.

B. Claims 10-18, 22-24, 27, 28 and 61-70 are pending and are the subject of this Office Action.

2. Specification

A. The specification is objected to since the priority data in the first line should be updated to reflect the fact that this application is a 371 of PCT/US2003/23241.

3. Claim Objections

A. Claim 66 is objected to since there should be a space between "about" and "5."

4. Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

A. Claims 10-18, 22-24, 27, 28 and 61-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. At least claim 10 recites a "drug lead." However, it is unclear what the meets and bounds of this term are, or how the term "lead" is defined.

B. Claims 10-18, 22-24, 27, 28 and 61-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. At least claim 10 recites "on *the activity*…" However, it is not clear as to what is this activity. The Examiner is of the position that the intended activity is to metabolize drugs. However, clarification is requested. Due to the potential complexity of amending the claim, at this time the Examiner only requests an explanation on the record as to what "the" activity is of the enzyme.

C. Claims 10-18, 22-24, 27, 28 and 61-70 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite that seeing a shift in the thermal curve in the presence of a co-regulator determines that the drug lead increases the activity of the enzyme. However, it is not clear as to which direction the drug lead shifts the curve. Therefore, it cannot be determined whether or not the activity of the enzyme is "increased."

D. Claims 12 and 28 recite the limitation "said target molecule." There is insufficient antecedent basis for this limitation in the claim, or in claim 10.

E. Claims 15, 17 and 23 recite the limitation "the molecule." There is insufficient antecedent basis for this limitation in the claim, or in claim 10.

F. Claims 15-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims recite "further modifies the stability of the receptor." However, it is not clear as to in which direction the stability is modified. Therefore, it is unclear how it can be concluded that a compound is an agonist, antagonist (e.g. "non-agonist") or partial agonist.

G. Claim 27 is confusing. The claim states that a non-agonist would not shift the thermal unfolding curve. However, claim 18 recites that a non-agonist can be a partial antagonist. However, it isn't clear how a partial agonist can shift the curve in one assay, yet have no effect in another.

H. Claims 62, 64-70 are confusing since it is not clear as to what the compound induces. Furthermore, it appears that in, for example, claim 62, that the agonist is already known to be a strong inducer. However, the point of the method step is to, in fact, determine the characteristic of the compound so it is unclear how the agonist is already known to be, e.g., a strong or weak inducer. If this is correct, the claims should be amended to read, for example, "...is determined to be a strong inducer," or "is determined to have a binding affinity of…"

4. Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

A. Claims 10-18, 22-24, 27, 28 and 61-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lustig et al (WO 99/27365) in view of Pantoliang et al. (WO 97/42500). The instant claims recite a method of identifying an agonist or antagonist of a co-regulator-dependent target molecule, namely nuclear hormone receptors, by measuring the effect of molecules on the thermal shift unfolding curve.

Lustig teach a method for identifying modulators of nuclear hormone receptors, which are known to affect p450 transcription, by combining the receptor and a candidate agent (Abstract). Lustig use a peptide sensor as a means of identifying the effect of the agent on the nuclear receptor in the presence and absence of the agent (Abstract; page 2, lines 5-21). The effect of this assay system is a cost-effective high-throughput screening of compounds which can bind the nuclear hormone receptor (including instant claims 37-40).

Lustig do not use a co-regulator. However, it would have been obvious to one of ordinary skill in the art at the time of the instant invention to have used a co-regulator in the method of Lustig since Lustig not only teach that these receptors bind to transcriptional co-activators (page 1, lines 16-17), but that the present invention "obviates the need to include a natural coactivator protein of the receptor in the mixture" (page 4, lines 20-21). This implies that a co-regulator (e.g. coactivator) would normally be used in a method of identifying ligands which affect nuclear receptors, though it is simply not required in Lustig. Lustig also do not teach the claimed method of screening compounds which can shift the thermal folding curve.

However, Pantoliano et al. do teach the exact method used in the instantly claimed invention (Abstract). The method of Pantoliano is used to screening a "multiplicity of different molecules for a target molecule which is capable of denaturing during a thermal change." The only difference between the method of Pantoliano and the instant invention is that Pantoliano use their assay to rank the affinity of the screened compounds, whereas the instant invention uses the assay to determine the potential of a compound to shift a functional (thermal) curve. The instant assay can be considered an assay to determine the rank order of potency. Though not the same as affinity, the two are related. Regardless, determining potency or affinity (agonists or antagonists) would be obvious variants as it is routine in the art when

characterizing receptors, or ligands, to determine both their binding (affinity) and functional (potency) capabilities. The methods are nearly identical except for the endpoint. The assay of Pantoliano is not limited to any particular target protein and can, therefore, include nuclear hormone receptors, which were well-known in the art to regulate p450.

B. Claims 10-18, 22-24, 27, 28 and 61-70 are rejected under 35 U.S.C. 103(a) as being unpatentable over Greenfield et al. (Biochemistry 2001) in view of Pantoliano et al. (WO 97/42500). The instant claims are discussed above.

Greenfield teach screening for ligand-dependent stabilization of ERa (Abstract). Though not specifically stated, Greenfield also teach the screening of agonists and antagonists since the last paragraph of the Abstract states that ERE can increase the thermal stability of ERa. Therefore, this method does identify either an agonist or antagonist (i.e. ERE).

Greenfield do not teach the use of a co-regulator; however, Greenfield do teach that co-regulators are known to be important in transcriptional activity of nuclear hormone (steroid) receptors. However, Greenfield do not teach the specifically recited methods.

However, Pantoliano et al. do teach the exact method used in the instantly claimed invention (Abstract). The method of Pantoliano is used to screening a "multiplicity of different molecules for a target molecule which is capable of denaturing during a thermal change." The only difference between the method of Pantoliano and the instant invention is that Pantoliano use their assay to rank the affinity of the screened compounds, whereas the instant invention uses the assay to determine the potential of a compound to shift a functional curve. The instant assay can be considered an assay to determine the rank order of potency. Though not the same as affinity, the two are related. Regardless, determining potency or affinity (agonists or antagonists) would be obvious variants as it is routine in the art when characterizing receptors, or ligands, to determine both their binding (affinity) and functional (potency) capabilities. The methods are nearly identical except for the endpoint. The assay of Pantoliano is not limited to any particular target protein and can, therefore, include nuclear hormone receptors, which were well-known in the art to regulate p450.

5. Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the “right to exclude” granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct

from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

A. Claims 10-18, 22-24, 27, 28 and 61-70 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over at least claim 1 of U.S. Patent 6,020,141; claim 1 of U.S. Patent 6,036,920; claim 1 of 6,214,293; claim 1 of U.S. Patent No. 6,232,085; claim 1 of U.S. Patent 6,268,218; claim 1 of U.S. Patent No. 6,291,191; claim 1 of US Patent No. 6,291,192 and claim 1 of U.S. Patent No. 6,303,322. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims recite methods of identifying agonists and non-agonists (e.g. partial agonist) by measuring the ability of molecules to shift the thermal unfolding curve of a target protein.

U.S. 6,020,141 recites nearly identical methods as the instant invention, the only major difference being that the patent is screening for rank order of affinity of each compound/molecule.

U.S. 6,232,085 recites nearly identical methods as the instant invention, the only major difference being that the patent is screening for rank order of efficacy of each compound/molecule.

U.S. 6,291,191 also recites nearly identical methods as the instant invention, the only major difference being that the patent is screening for rank order of affinity of each compound/molecule.

U.S. 6,291,192 also recites nearly identical methods as the instant invention, the only major difference being that the protein is produced by recombinant DNA technology before the effect of test molecules on the thermal folding curve is determined.

U.S. 6,303,322 recites a method of generating lead compounds. However, this method recites that this procedure is performed by identifying compounds which are able to bind to a receptor (i.e. target) molecule by determining the ability of the compounds to shift the unfolding curve of the protein. In fact, the methods of the patent are nearly identical to that of the instant invention. The patent requires these

molecules to be produced, whereas the instant invention uses known molecules/compounds. Other than that, there are no significant differences in the method steps.

Therefore, it would have been obvious for one of ordinary skill in the art at the time of the instant invention to have used the methods of the patents to identify ligands which bind to any type of protein (i.e. target molecule). The method of the patents shows that the effects of compounds or molecules on a protein can readily be determined by using the method steps to determine which compounds shift the curve. These methods should work regardless of which protein is being studied. The fact that the instant application requires a co-regulator would not affect the obviousness, since proteins and their co-regulators are well known in the art. Their use would be obvious in testing the effect of compounds on the target protein.

The instant application uses these same procedures to identify molecules which affect the thermal folding curve of a target molecule. The fact that the patents measure the rank order of affinity, or efficacy, of the compounds while the instant invention is silent to this measurement still does not render the instant invention non-obvious since the method steps of the patent and instant application are nearly identical, the major difference being that the patent places these compounds in order, which would be obvious since the instant application would already have this data obtained from its studies using the claimed method.

U.S. 6,036,920; U.S. 6,214, 293; U.S. 6,268,218 -

U.S. 6,268,218 recites nearly identical methods as the instant application. U.S. Patent 6,036,920 and U.S. 6,214,293 recite an apparatus for measuring the effect of compounds on the thermal folding curve of proteins. The only major difference between these patents and the instant invention is that the '920 and '218 patents use fluorescence. However, fluorescence is a well-known means of detecting the effects of a compound on a protein. The fact that the instant application used binding studies instead of fluorescence does not render the instant invention non-obvious. U.S. 6,036,920 uses a computer to determine the shift in the thermal curves. However, the use of a computer to perform calculations also does not render the instant invention non-obvious. Both the '920 and '293 patents are product claims. The instant invention is basically a method of using the patented product.

B. Claims 10-18, 22-24, 27, 28 and 61-70 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over at least claims 1 of copending Application Nos. U.S. 2002/0114734; U.S. 2003/0175813; U.S. 2003/0203497; U.S. 2004/0185504; U.S. 2006/0024844 and U.S. 2006/0110732. Although the conflicting claims are not identical, they are not patentably distinct from each other.

The instant claims recite methods of identifying agonists and non-agonists (e.g. partial agonists) by measuring the ability of molecules to shift the thermal unfolding curve of a target protein.

U.S. 2003/0175813 recites nearly identical methods as the instant invention, the only major difference being that '813 is screening for rank order of affinity of each compound/molecule.

U.S. 2002/0114734; U.S. 2003/0203497 and U.S. 2004/0185504 appear to be the apparatus used for determining thermal folding curves. Therefore, the instant method claims are simply a method of using the product of the '734, '497 and '504 applications. As discussed above in paragraph A, the use of fluorescence to detect the effect of compounds on a protein would have been simply another obvious means of detecting the effect of compounds on that protein.

Therefore, it would have been obvious for one of ordinary skill in the art at the time of the instant invention to have used the methods of the copending applications to identify ligands which bind to any type of protein (i.e. target molecule). The method of the copending applications show that the effects of compounds or molecules on a protein can readily be determined by using the method steps to determine which compounds shift the curve. These methods should work regardless of which protein is being studied. The fact that the instant application requires a co-regulator would not affect the obviousness, since proteins and their co-regulators are well known in the art. Their use would be obvious in testing the effect of compounds on the target protein.

The instant application uses these same procedures to identify molecules which affect the thermal folding curve of a target molecule. The fact that the copending applications measure the rank order of affinity, or efficacy, of the compounds while the instant invention is silent to this measurement still does not render the instant invention non-obvious since the method steps of the copending applications and instant application are nearly identical, the major difference being that the copending applications place these compounds in order, which would be obvious since the instant application would already have this data obtained from its studies using the claimed method.

U.S. 2006/0024844 recites basically the same methods as the instant application. The major difference is that the '844 application does not recite that the a receptor regulating p450 is used. However, the method steps are essentially identical. As discussed in the above rejection under 35 USC 103, it would have been obvious at the time of the instant invention to have used the method of '844 to study any protein, including receptors.

U.S. 2006/00110732 recites nearly identical methods as the instant application. The only difference is that the '732 application recites that the method is used to determine the tissue selectivity of a ligand for a co-regulator-dependent target molecule. Since the methods are basically identical, it would have been obvious to one of ordinary skill in the art to have used co-regulators from different tissues to determine selectivity. Co-regulators for target proteins are well known. Furthermore, the instant invention does not rule out using tissue-selective co-regulators.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

6. Conclusion

A. No claim is allowable.

Advisory information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert Landsman whose telephone number is (571)272-0888. The examiner can normally be reached on M-F 10 AM – 6:30 PM (eastern).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Robert Landsman/
Primary Examiner, Art Unit 1647